Table III. Antimalarial Testing Data (*P. berghei* in Mice)

Compd	Dose, mg/kg	Mean survival time, days[a]	Δ survival time, days	Mortality
8	20	6.6	0.4	5/5
	40	7.0	0.8	5/5
	80	10.0	3.8	5/5
	160	16.6	10.4	5/5
	320	19.6	13.4	5/5
	640	20.2	14.0	5/5
9	20	6.4	0.3	5/5
	40	6.4	0.3	5/5
	80	6.6	0.5	5/5
	160	9.6	3.5	5/5
	320	14.0	7.9	5/5
	640	14.8	8.7	5/5
12	20	6.4	0.3	5/5
	40	6.4	0.3	5/5
	80	6.6	0.5	5/5
	160	6.6	0.5	5/5
	320	7.0	0.9	5/5
	640	18.4	12.3	5/5
16	20	6.2	0.1	5/5
	40	6.4	0.3	5/5
	80	6.4	0.3	5/5
	160	9.6	3.5	5/5
	320	10.8	4.7	5/5
	640[b]	16.0	9.9[c]	

[a]Mean survival time of controls: 6.2 for **8**; 6.1 for 9, 12, and 16. [b]Four mice survived for 60 days; mice which survive for 60 days are considered cured. [c]Data for uncured mice.

preparation of **15** was also conducted in the presence of 2 equiv of pyridine in refluxing DMF for 3 hr. Similar results were obtained, and the yield was only slightly improved. The procedure employed for preparing 1,3-bis[3-(3-trifluoromethylphenyl)-1,2,4-oxadiazoyl]-benzene (**20**), which is the same as that employed for **17**–**19**, is as follows. To a solution of 3.5 g (0.017 mole) of **25** in 50 ml of dioxane and 1.4 g (0.017 mole) of pyridine was added a solution of 1.7 g (0.0085 mole) of isophthaloyl chloride in 50 ml of dioxane. After refluxing for 18 hr, the hot solution was decanted from a red oil, and the dioxane was removed *in vacuo*. Analytical purity was achieved by two reprecipitations from dioxane by H_2O.

Acknowledgment. The authors wish to thank Dr. Edgar A. Steck of the Walter Reed Army Institute of Research for many helpful discussions during the course of this work.

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Book Reviews

Iatrogenic Diseases. P. F. D'Arcy and J. P. Griffin. Oxford University Press, London, New York. 1972. vi + 208 pp. 24.5 × 19 cm. Cloth $19.95. Paperback $13.50.

Adverse reactions are encountered with every drug and with almost every nutrient in a certain proportion of individuals. In some cases, doses of drugs approaching toxic levels must be used to achieve therapeutic success; in other cases, reaction to a drug is genetically determined. Hepatic or renal disease can interfere with metabolism and excretion of normal doses of drugs, and thus increase the retained drug concentrations to toxic amounts. Some individuals have a low threshold to normal pharmacological actions of drugs. Others develop hypersensitivity with ensuing pathological symptoms, or idiosyncrasy to a given class of agents. When drug combinations are used in therapy, one drug may suppress the hepatic microsomal enzymes needed for the metabolic removal of the other agent(s). Or else, a drug may induce biosynthesis of such enzymes, which leads to increased rates of metabolism of the other agent in the combination, sometimes with catastrophic physiological results. Even the metabolism of many foods is influenced by various drugs.

The clinically observable symptoms of all these adverse reactions are called iatrogenic diseases. The present volume presents a summary of the epidemiological aspects of iatrogenic disease, and gives a fully documented report on all types and cases of drug-induced pathology listed in the medical literature. The adverse reactions are arranged according to the organ or tissue where they are manifested. Biochemical causation is stressed wherever possible. Generic drug names are used in the text but a convenient and comprehensive cross index to American, British, and Continental proprietary drug names is appended. The book should be of the greatest value to medical practitioners, but it will serve pharmacologists and biochemists equally well. It should also be read by drug safety administrators and trial lawyers because it lists toxic reactions clearly but places their incidence in proper perspective in regard to the therapeutic advantages of each drug.

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Chemical Oxidations with Microorganisms. By Gunther S. Fonken and Roy A. Johnson. Marcel Dekker, New York, N. Y. 1972. vii + 292 pp. 17 × 24 cm. $19.50.

The organic chemist who lacks microbiological training will be glad to find, in the concluding chapter of this book, detailed directions for experimental procedures for reactions involving microbial cultures. All too often chemists are deterred from undertaking exquisitely specific and stereospecific microbial oxidations because they do not have the "feel" for such operations. The equipment, its sterilization, the securement and use of the cultures, solvents, and reaction and work-up methods are all set forth with great clarity.

The body of the book discusses 12 types of microbial oxidations, according to the structures of the substrates. They include hydroxylation of nonactivated carbon bonds, allylic, olefinic, and aromatic hydroxylations, aromatic ring opening, Baeyer–Villiger and β-oxidations, dehydrogenations, oxidation of amines, sulfur compounds, oxidative dealkylations, etc. All reactions are richly illustrated and referenced. It will not be surprising if this book serves as a catalyst to draw many organic chemists to the use of microbes as chemical reagents.

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Advances in Drug Research. Vol. 6. Edited by N. J. Harper and A. B. Simmonds. Academic Press, London, New York. 1971. vi + 256 pp. 23.4 × 15.7 cm. $15.00.

This volume contains four excellent reviews. Two of them are essentially pharmacological, namely, Activities and Sites of Antinociceptive Action of Morphine-like Analgesics (by A. Herz and A. J. Teschemacher) and Molecular Aspects of the Storage and Uptake of Catecholamines (by N. Kirshner, S. M. Schanberg, and R. M. Ferris). Another review deals with Mass Spectrometry in Drug Research (by B. J. Millard). It reexplains briefly principles and scope of mass spectroscopy and selects as illustrative examples relatively

complex drug structures, alkaloids, antibiotics (including peptide antibiotics), drug metabolites, the analytical detection of impurities in drugs, and forensic and toxicological applications. The most important contribution to the volume is, however, a discussion of Principles and Practice of Hansch Analysis: A Guide to Structure–Activity Correlation for the Medicinal Chemist (by M. S. Tute). In unusually simple and understandable English it leads the reader through the mathematics and principles of the field. Of great value are tables of physical constants widely used as parameters in Hansch analysis. They include π values, log P, σ, E_R, dipole moments, bond refraction (α), and steric parameters (E_S) for various systems. The need for quantitative study of hydrophobic, steric, and a multitude of electronic effects by multiple regression analysis is stressed, if the forces underlying intrinsic drug activity are to be understood without knowing anything about drug receptors. These calculations help us to understand transport, metabolism, excretion, and apparent discrepancies between *in vitro* and *in vivo* activities. Selectivity, dependent largely on log P, can be predicted, and if a sufficient number of members of a given series of compounds can be studied, many other drug characteristics can be projected for as yet unknown analogs. Too few users of Hansch analysis have included steric parameters whose importance is beginning to emerge. The future of this approach will look brighter if one and the same group of investigators would carry out the biological test of a group of related compounds, coordinate further synthesis with test results, and carry out multiple regression analysis themselves.

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Fluorocarbon and Related Chemistry. Vol. 1 (one of the series "Specialist Periodical Reports"). R. E. Banks and M. G. Barlow, Senior Reporters. The Chemical Society, Burlington House, London, England. 1971. viii + 307 pp. 13.5 × 21.5 cm. £7.00 (£4.00 to members of Chemical Society).

The publication of this first volume in a projected series of biennial reviews on the chemistry of organic, organometallic, and organometalloidal fluorine-containing compounds will be welcomed by all investigators in this area of research. The emphasis is on compounds having a relatively high proportion of C–F bonds.

The purpose of the volume is to review the literature published during 1969 and 1970. With the enormous growth and proliferation in this field, the authors have faced an enormous task, but they have met the challenge and succeeded admirably.

The format of the book closely resembles that of the well-known *Annual Reports of the Chemical Society*, with the liberal inclusion of structural formulas, reaction sequences (as Schemes), and tables, all of which markedly increase the value to the reader. The text consists of six chapters which include, in sequence, saturated fluorocarbons, fluorocarbon hydrides and halides; per- and polyfluorinated olefins, dienes, ketenes, and acetylenes; aliphatic polyfluorinated carbonyl compounds; polyfluoroalkyl derivatives of the elements (100 pages); polyfluorinated aromatic compounds; and a useful chapter on significant progress in ^{19}F nuclear magnetic resonance spectroscopy. In addition, there is a valuable appendix listing recent books and major reviews and a second appendix of miscellaneous publications concerned primarily with spectroscopic properties of fluorinated compounds.

The authors are to be congratulated for a remarkably thorough coverage of the literature. The text is chock full of goodies for anyone interested in these compounds, but, in keeping with the authors' intent, there is little critical evaluation of the results reported. When indicated in the original article, mention is made of applications in medicinal and biological chemistry.

The printing is excellent and I noted only a few minor errors. This book should be on the shelf of anyone active in fluorocarbon research. We will look forward with great interest to the second volume in this series.

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Cyclic AMP and Cell Function. Edited by G. Alan Robison, Gabriel G. Nahas, and Lubos Triner. New York Academy of Science, New York, N. Y. 556 pp. 15 × 22.9 cm. Paperback, $29.00.

In short succession, the group around Earl W. Sutherland has compiled a second monograph on cyclic AMP (see G. A. Robison, R. W. Butcher, and E. W. Sutherland, *Cyclic AMP*, Academic Press, New York, N. Y. 1971), this time a multiauthored account of a symposium. The role of cyclic AMP as an intracellular mediator of the actions of a large number of amine and polypeptide hormones and thereby as a regulator of diverse metabolic functions is too well known to require review. But many facets of the role of cyclic AMP are still more or less obscure. Among them are the relation and timing of the catalytic and hormone-stimulated activities of adenyl cyclase, the functions of GTP or GDP, the detrimental effects of cell breakage on the enzyme, the effects of fluoride and calcium ions, the role of phosphodiesterase, and particularly the mechanisms by which permissive hormones may affect cyclic AMP. Some, although not all, of these topics are dealt with in the present symposium volume. Not included are effects of cyclic AMP in microbiology and in clinical studies. Hopefully these subjects will be reviewed at a later date. The present monograph will enable the reader to get an up-to-date and well-referenced view of the biochemical and pharmacological state of this rapidly expanding field.

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Butyrophenones in Psychiatry. Edited by Alberto DiMascio and Richard I. Shader. Raven Press, Hewlett, N. Y. 1972. 128 pp. 15.5 × 23.3 cm. $9.75.

Of the *ca.* 1500 butyrophenone derivatives and analogs synthesized and tested, principally by Paul Janssen, less than 10 were introduced as clinical antipsychotic drugs in Europe. In this country, haloperidol has made the grade, while one or two analogs are still in clinical trial. As with so many other drugs, the butyrophenones have been hailed as the beginning of a new era in clinical psychopharmacology and shrugged off as just another group of palliative antipsychotics. The truth, as always, lies between such extreme views. Haloperidol, the best-studied drug in this series, is useful in the treatment of manic patients and especially of Gilles de la Tourette's syndrome. It is also effective in psychotic geriatric patients, being a cut above or equal to standard phenothiazine tranquilizers. The extrapyramidal side effects of haloperidol are of the same order as those found with potent phenothiazines. Haloperidol appears to be a more specific and potent blocker of central dopaminergic synapses and produces less sedation and autonomic side effects than thioridazine and chlorpromazine.

The present small book is addressed to the scientifically trained practicing psychiatrist. It details "cook-book" directions for treatment of various classes of patients, but gives also structure–activity relationships of butyrophenones and pharmacological information on uses, side effects, and unusual clinical applications. The practitioner will appreciate the lucid style and explanations written by outstanding psychiatrists.

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Methods in Molecular Biology. Vol. 2. Protein Biosynthesis in Nonbacterial Systems. Edited by Jerold A. Last and Allen I. Laskin. Marcel Dekker, Inc., New York, N. Y. 1972. xi + 336 pp. 23.5 × 16 cm. $16.50.

This is the second in a series of volumes intended to provide "cookbook" directions for neophytes to molecular biology. By and large this objective is realized in that in all but one chapter (that dealing with the preparation and mode of action of interferon) the methodologies and techniques are described clearly and in detail. Lab jargon, where used, is first explained. In order to make the volume both current and inexpensive it has been printed by an offset method, but unfortunately neither of these objects was met. First of all, the majority of the contributions appear to have been completed early in 1971 while the volume did not appear until the following year. Secondly, the cost per word seems high in comparison to other similar volumes which have been printed by conventional means.

This volume concentrates on the practical aspects of the preparation and properties of protein-synthesizing and related systems obtained from nonbacterial sources. (The bacterial systems were treated in the first volume of the series.) Descriptions of protein-synthesizing systems derived from a variety of mammalian tissues plus descriptions of the preparations of hemoglobin mRNA and reticulocyte initiation factors comprise the majority of the book. The remainder of the book deals with protein-synthesizing systems

from wheat embryo and paramecium and a final chapter on interferon which appears completely out of place because it is written simply as a literature review.

While the present volume contains a number of shortcomings including organization and topic selection, it none the less provides a reasonable starting place for a newcomer to protein synthesis in nonbacterial systems.

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The Alkaloids. Vol. 2. J. E. Saxton, Senior reporter. Specialist Periodical Report of the Chemical Society, London. 1972. ix + 293 pp. 13.5 × 21.5 cm. £7.50 ($19).

This book is the second volume of a yearly review of the chemistry of the alkaloids to be published by the Chemical Society, covering the literature from July 1970 to June 1971. Two-thirds of this volume has been written by J. E. Saxton (University of Leeds) and V. A. Snieckus and H. O. Bernhard (University of Waterloo, Canada), and they have covered the chemistry of pyrrolidine, piperidine, pyridine, tropane, pyrrolizidine, indolizidine, quinolizidine, quinoline, quinazoline, acridone, β-phenethylamine, isoquinoline, Amaryllidaceae, Erythrina, Lycopodium, and miscellaneous alkaloids. The rest of the book has been written by persons who are actively engaged in research on the subject matter of their chapters: biosynthesis by J. Staunton (Cambridge University), indole alkaloids by J. A. Joule (University of Manchester), diterpene alkaloids by S. W. Pelletier and L. H. Wright (University of Georgia), steroidal alkaloids of the Apocynaceae and Buxaceae by F. Khuong-Huu and R. Goutarel (Gif-sur-Yvette). The only group of alkaloids which have been intentionally omitted are the *Solanum* and *Veratrum* steroidal ones.

In general, the coverage is good and complete, and there are numerous structural formulas. Long synthetic sequences leading to complex alkaloid structures are well presented, the reagents used in the various steps being given in footnotes. Several errors were discovered. On p 21, references 53 and 54 in no way relate to the biosynthesis of anabasine. On p 36 campedine (9) lacks on OH group in the benzene ring. Compound 17, p 37, is not related to anaferine, but to arecoline. Caffeic acid (3,4-dihydroxycinnamic acid) has nothing in common with caffeine, except that they have both been isolated from the coffee plant. Neophytes may be misled into believing that tobacco is a source of caffeine as well as nicotine (p 273, ref 14, *cf.* also ref 17)! The new alkaloid (49), p 282, is damascinine, not damascenine.

There is an author index, but no subject index, which is disappointing and frustrating. It is relevant to compare these yearly specialist periodical reports on the alkaloids with the well-established series published by Academic Press, entitled, "The Alkaloids," edited by R. H. F. Manske. These volumes appear about every 18 months; however, each volume does not attempt to cover the whole field. Thus the review of a certain class of alkaloids will usually cover the literature of several years, and a more critical and complete account can be written. In conclusion, I recommend purchase of the present volume, especially at the reduced rate available to Fellows of the Chemical Society, to all those interested in the chemistry of natural products. They will be exposed to many novel synthetic reactions and intriguing structures, many of which are worthy of biosynthetic investigation.

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Organophosphorus Chemistry. Vol. 3. Edited by S. Trippett, with 8 contributors. The Chemical Society, London. 1972. x + 303 pp. 14 × 21.5 cm. £7.00 ($17.50).

This work, one of a continuing series of Specialist Periodical Reports published under the auspices of The Chemical Society, constitutes a review of the literature of organophosphorus chemistry published between July 1970 and June 1971. Approximately 1300 papers are reviewed in highly readable style, and the authors appear to have made an excellent choice of materials to be presented. The work contained has a Western flavor, but coverage of the Russian literature is adequate.

The book contains eight chapters primarily of chemical interest, covering phosphines and phosphonium salts, quinquecovalent phosphorus compounds, halogenophosphines, phosphine oxides and sulfides, tervalent phosphorus acids, quinquevalent phosphorus acids, ylides, and phosphazenes. Each is organized by classes of compounds, so that information of interest can be found easily. In each section, synthetic methods, reactions, and miscellaneous information are presented sequentially.

Papers concerned with uses of spectroscopy and other physical methods are grouped together in a highly useful separate chapter, as are reports involving radical, photochemical, and deoxygenation reactions. There is also a chapter on phosphates and phosphonates of biochemical interest, which provides a uniquely thorough look at this important and rapidly developing field. An author index is provided.

The book is remarkably timely for a printed volume and should be of interest to any chemist at all concerned with organophosphorus chemistry.

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PMR Spectroscopy in Medicinal and Biological Chemistry. By A. F. Casey. Academic Press, New York, N. Y. 1971. xvi + 425 pp. 15 × 22.8 cm. $23.00.

Advances in nmr instrumentation have prompted a recent surge in the investigation of nuclei other than proton (especially ^{13}C). It is, therefore, a highly appropriate time to discuss major contributions of pmr spectroscopy, which has been such a prolific field over the past 15 years and remains the single most important instrumental technique to so many chemists interested in a variety of structural problems. A. F. Casey is an expert in the area of the application of pmr to the elucidation of stereochemical and conformational aspects of organic molecules. In writing this book, he has assumed that the reader has a knowledge of the fundamentals of nmr and has adopted an effective instructional rather than review approach. The material is well organized and effectively presented with extensive bibliographical data (to 1970) accompanying each chapter. In the first half of the book (Chapters 1–5) the author presents a comprehensive discussion of general principles, many of which are applied to specific examples of pharmacological and biochemical interest in the second half. Chapter 1 deals with analytical aspects including analyses of pharmaceuticals and reaction product mixtures, as well as the qualitative usefulness of alcohols and aromatic derivatives. The unique pmr features of organic nitrogen compounds are the topic of the following chapter. This information is prerequisite to an understanding of the spectra of nitrogen-containing biochemicals and drugs. Chapter 3 is devoted to stereochemical subjects including olefinic and diastereomeric compounds, anisotropic effects, NOE, and a discussion of conformational free energy. The pmr spectroscopy of cyclic-nitrogen-containing compounds is the subject of Chapter 4, while Chapter 5 covers optical enantiomorphs. The next two chapters deal with pmr studies of narcotic analgetics, cholinergic agonists, histamine, antihistamines, tropanes, sympathomimetic amines, antibiotics, and steroids. The concluding two chapters are devoted to studies of amino acids, peptides, proteins, carbohydrates, nucleotides, and nucleic acids. Relaxation time studies of protein conformation and intermolecular association are also included. This reviewer highly recommends the book for general use by graduate students and practicing chemists in the areas of organic and medicinal chemistry, as well as by those biochemists and pharmacologists with interests in biomolecular conformation and drug–receptor interactions.

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